Pancreatic beta-cell neogenesis by direct conversion from mature alpha-cells.

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Public Summary:
Because type 1 and type 2 diabetes are characterized by loss of beta-cells, beta-cell regeneration has garnered great interest as an approach to diabetes therapy. Here, we developed a new model of beta-cell regeneration, combining pancreatic duct ligation (PDL) with elimination of pre-existing beta-cells with alloxan. In this model, in which virtually all beta-cells observed are neogenic, large numbers of beta-cells were generated within 2 weeks. Strikingly, the neogenic beta-cells arose primarily from alpha-cells. alpha-cell proliferation was prominent following PDL plus alloxan, providing a large pool of precursors, but we found that beta-cells could form from alpha-cells by direct conversion with or without intervening cell division. Thus, classical asymmetric division was not a required feature of the process of alpha- to beta-cell conversion. Intermediate cells coexpressing alpha-cell- and beta-cell-specific markers appeared within the first week following PDL plus alloxan, declining gradually in number by 2 weeks as beta-cells with a mature phenotype, as defined by lack of glucagon and expression of MafA, became predominant. In summary, these data revealed a novel function of alpha-cells as beta-cell progenitors. The high efficiency and rapidity of this process make it attractive for performing the studies required to gain the mechanistic understanding of the process of alpha- to beta-cell conversion that will be required for eventual clinical translation as a therapy for diabetes.

Scientific Abstract:
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